

## THOUGHT OF A NONMILLENARIAN

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As a scientist, I am not much inclined to think about the mystical or mythical significance of dates. But some years ago, I awoke to the power of such ideas after reading one of Václav Havel's stirring speeches (July 4, 1994, The Measure of Man), a speech that received much attention. Havel joined his concerns about contemporary society to the forthcoming end of the millennium in ways I found disturbing. He described the approach to the millennium as a "transitional period," a time when "all consistent value systems collapse" when "everything is possible because our civilization does not have its own spirit". And Havel held science responsible. You can understand my concern.

Besides tying the world's troubles to science, Havel's thoughts stirred me for another reason. As a child, my religious school teachers had been at some pains to stress that the year one, in the common calendar, was an adopted convention of no particular significance. I was taught that for the years before 1, we counted backwards and labeled them B.C.E.--Before the Common Era. We thus lived in the Common Era - whatever that was. I was left to figure out for myself why in public school they used the same numbers but different abbreviations...B.C. and A.D. It took me some time to do that. To make matters worse, I was taught another yearly numbering system, one that appears on all Jewish calendars and on Rosh Hashonah notices from my synagogue. It starts with the beginning of the world, calculated back from the biblical generations, making the current year 5757. Why do Havel, and others, then place such importance on a number of no special consequence?

Actually, by the time of Havel's speech I already knew that the year 2000 might inspire some fuss. Foreseeing the destructive potential of millenarian thinking, A. Bartlett Giamatti, then president of Yale had earlier warned us, in his typically eloquent prose, to be wary.

“ I believe that the new wisdom of a century's end is really only fatigue masquerading as philosophy. I urge you to beware the captivation of these easy, thoughtless profundities. These banalities have only in common the belief that we are not able to give definition--shape and contour--to what is around us. These shibboleths finally tell more about those who utter them than about reality. They are expressions of exhaustion more often than they are forms of explanation.”

Giamatti here gives us a charge: to try to give definition --shape and contour--to what is around us. And that is what I shall attempt, at least with respect to science and technology. Far from being dead, or even suffering from exhaustion, science and technology are spirited and robust. They compel us to inquire about our current and foreseeable relations with the natural environment, which includes ourselves, other living things, our planet, and the vast universe beyond. They also compel us to consider our relations with the external environment we construct for ourselves through technology.

We will bring into the 21st century knowledge about these environments that is unprecedented in scope and depth. This has nothing to do with the new millenium. It is, to large extent, the consequence of the far-reaching and enlightened support of fundamental scientific research by the U.S. government over the past 50 years. Our knowledge is deep enough to give us considerable control over many aspects of nature,

including our own lives and deaths. It is powerful enough to allow us to preserve or destroy the very environment that supports us and gave us birth.

These are powers that we have sought. They can be used for good and misused for evil. But they are not all-powerful. There remain strong, eternal forces within ourselves and in the natural world that remain difficult or impossible to control.

Our vast, accumulated knowledge of the natural world will inform what we make of the future. But though it is vast, it is also very incomplete; our ignorance is great. Indeed, part of our knowledge is the recognition of things we don't know now, but can anticipate adding to our store in the coming years; I will be talking about some of these for most of my time. This class of unknowns was described by Woody Allen:

"There is no question that there is an unseen world. The problem is, how far is it from midtown, and how late is it open?"

But the future will also bring answers to some questions we haven't asked yet. A future Woody Allen may even be driven to wonder if there are places besides Manhattan. We can glean an idea of the potential of what we don't know we don't know from some concepts that were unimaginable at the start of the 20th century. The internal workings of atoms were unknown; one clue, the existence of x-rays, was discovered just before the new century began. No one knew that they didn't know about quantum physics or relativity. Yet, from these discoveries came such a profound concept as the interchangeability of matter and energy and thus nuclear energy and nuclear weapons as well as semiconductor technology and the lasers that make so much of contemporary technology possible. A hundred years ago, the word "computers" meant the women employed to do calculations for astronomers. We didn't understand that our sun is only a

modest star in a galaxy of billions of stars that is itself only one among billions of galaxies in a universe that is not only beyond our ken in size but getting bigger all the time.

We didn't know anything about viruses or antibiotics. Genes didn't have a name, no less a chemical definition. The structure and significance of very large molecules, like DNA and proteins, was as enigmatic as are black holes today. And the list goes on and on.

The future will bring its own surprises because we know with a great deal of certainty that there will be among us people of imagination, creativity, and skill who will formulate the unasked questions and translate the new knowledge into new technologies. The world that is coming will seem as strange to us as ours would be to our great grandparents. California, for them, was still a place for adventurers. Nowadays we all go to California to see our kids. Will our grandchildren have to go to Mars to see theirs?

Because of the things we don't know we don't know, the future is largely unpredictable. But there are some things we can foresee because they are developments anticipated or at least imaginable from knowledge already in hand.

Common sense says that what we see is what there is. But in this instance common sense and some philosophers are wrong. We can only see what our eyes evolved to see. They are magnificent devices, but limited. Technology lets us see much more. With TV we see in real time, things in far away places. With microscopes, we see beautiful things too small for our eyes. As microscopes get smarter, smaller and smaller things come into view. In the 21st century, we may well get a direct look at atoms.

Telescopes allow us to see further and they too get better all the time. Space telescopes like Hubble and enormous new telescopes on Earth see more and more distant galaxies....galaxies so distant that their light took billions of years to reach us. We can know those galaxies only as they once were, and they tell us about the early history of the universe. With some microscopes and telescopes we see things that are invisible to us because our eyes are insensitive to infrared, ultraviolet, x-ray, and radio frequency radiation. And then there is a lot of stuff out in the universe that we can't see at all because it's dark. We know it is there only because of its gravitational effects. How much dark matter is there? Some say it could represent as much as 90 percent of all the matter there is. The answer to this question will determine whether the universe will continue to expand or collapse back to a singularity of some sort or just hang-in there at some size. When will we learn what that strange dark matter is? Is it some entirely new kind of stuff? And if it is, will we find uses for it? Will it change our lives?

Meanwhile, astronomers lives, like everyone else's, are being changed by computer technology and hi-tech light collectors called charge-coupled devices (CCDs). Though it is not as romantic as a freezing cold telescope dome on an isolated mountain, astronomers in their warm offices continents away can now control telescopes on the planet or in space and collect the data with computers. Even high school students have access to astronomical observations directly by computer and learn firsthand about research.

Astronomers and other scientists were the first to come to depend on the internet. Now, no one can imagine doing research or business without constant communication with colleagues world-wide. And this is catalyzing an interesting cultural revolution: the use of English as the world's common language. This could be an enormous force for unexpected developments. At least two countries are already frightened enough to take

steps to counter this revolution. France insists that home pages and information originating from that country be in French, even when the source is an American university outpost. Iranians have no access to the internet at all because of their government's well-founded worries about the influences of American language and culture.

Much closer to home than other galaxies or stars are the planets, moons, and roaming objects of the solar system. The sun and about 4.5 billion years of history bind us all together. In the future, people will forget a lot of the events we daily find so compelling. But they will remember that in our time, for the first time, our species visited Earth's moon, and sent surrogate visitors to other planets. What distant place will be next for us? Will we go back to the moon? Will we walk on Mars? If so, we must first learn to protect travelers from weightlessness, and from the intense radiation they will encounter on the way. And such voyages will depend on our willingness to spend a great deal of money. Right now we don't seem very bold or confident in our wealth....we seem to have lost our nerve. Will that change?

Our interest in Mars was revived a few months ago when a group of scientists published surprising conclusions about a very ancient (4.5 Ga) piece of Mars that had been lying around in Antarctica for 13,000 years; according to their interpretation of their investigations, living things once inhabited Mars. A lot of scientists, including myself, are skeptical. Earlier evidence from the Viking probe of Mars' surface seemed definitively negative on this question, although the conclusion now seems less certain. Chances are that we will want to settle the matter, fairly soon, with better and deeper searches on the red planet and we'll want to have a look at the possibility of life on Europa, a moon of Jupiter and other watering places in the Solar System. The quest will seem boring and uselessly expensive if the answer is NO, but it's hard to imagine

anything more earth-shaking than discovering we have company in the universe even if it is only microbes.

It's not surprising that a couple of random samples from Mars don't constitute a satisfactory search when we are still discovering life of unanticipated kinds and in unexpected places on Earth. In the last 25 years, a whole new class of organisms, the archaeobacteria, was discovered. To our astonishment, we've learned that bacteria live deep within the rocks under Earth's surface apparently as deep as 200 meters. It's only in the last 20 years that we have discovered strange organisms, and not only bacteria, but worms and shrimp, living in what we thought would be inhospitable environments at the deep sea hydrothermal vents where the margins of the great rocky tectonic plates spread apart and material and heat spew out from deep within the Earth. Other unusual bacteria live in the fluids bubbling out of the earth at the smelly hotspots like those that fascinate us at Yellowstone. These bugs, and some at the submarine hydrothermal vents evolved to live at temperatures we used to think impossible for life. Their chemistry is clearly related to ours, as expected if we are distant cousins. But they don't wilt in the heat, like we do. Their proteins and enzymes differ enough from ours to make them efficient even at temperatures above the boiling point of water. Already, we have made use of some of their enzymes; one of them is an essential tool in the methods used to determine the DNA sequence of genomes, and to detect human mutations related to disease.

It is a great frustration that we can see out into the universe, but we can't see into our own home planet. 'Seeing' below the surface layers of the Earth now depends largely on sophisticated analysis of seismic waves. Yet, we ought to know much more about the shifting tectonic plates that lie under the Earth's surface, and the processes in the underlying mantle and core if we are ever to be able to do a decent job of predicting earthquakes or volcanic eruptions.

Even without such fundamental knowledge it is now apparent that existing seismological instruments can pick up phenomena that are characteristic precursors of volcanic or earthquake activity. If sufficient numbers of instruments were deployed in strategic places we might be able to predict at least some of these catastrophes at times early enough to be useful.

New insights into our planet are acquired from laboratory experiments under conditions that simulate the deep earth. These studies are showing us that atoms we thought we understood take on unusual properties at high temperatures and pressures. Thus, fundamental studies in earth science are evolving into new chemistry and physics, and who knows what new, amazing materials that can be used for innovative purposes.

Our planet includes more than the solid earth on which we stand. The atmosphere is part of the system as we are well aware when severe storms and serious flooding occur. Like earthquakes and volcanic eruptions we have no control over these natural events. But it would be enormously helpful if they could be predicted well ahead of onset. Methods for short-term, reliable predictions are neither available or likely in near future. But we're beginning to see the possibility of better understanding of weather on time scales as long as decades. Few problems are more complex, or more hampered by a lack of adequate technology or investment. Relevant factors include oceans and their surface temperatures and circulation, global atmospheric circulation, and populations of organisms, most particularly green plants and ourselves.

The connection between green plants and atmospheric conditions - that is, the extent to which the composition and circulation of the atmosphere depend on exchanges of CO<sub>2</sub>, O<sub>2</sub>, and water by plants - reminds us of the intimate relations between the



physical earth and the biosphere. Increasingly we recognize that we need to know much more about each of these two worlds, and of their interactions, if we are to maintain the planet as an hospitable environment for our own species.

Among other things, we will have to decide how much more we want to know about the uncounted number of species that share Earth with us. In the past we could, without penalty, remain ignorant of most of them. No more. It is now too easy for us to destroy some organisms on which, unknown to us, we and our planet depend...or might in future find useful. The evolutionary history of our species...our cultural as well as biological evolution, has made us highly dependent organisms. We like to think that because we're powerful, we're in charge. But we are not.

For example, we evolved to breath oxygen, although oxygen was not an original component of Earth's atmosphere. It was, and is, put there by algae and plants. We are totally dependent on green plants for other essentials as well. Newly grown plants provide clothing and shelter and food to supply the energy we need to run the machines that are our bodies. The cooked remains of ancient plants give us energy sources in the form of coal and oil to run the machines that we build. Up to the present, the only truly efficient way to capture the energy of the sun has been through the intermediary of green plants. In spite of a lot of effort, the technology we have for direct capture of the sun's energy is only of limited utility--on satellites, but not on Earth. This could change in the foreseeable future. We need to find alternative energy sources not only because what we have is limited, but because the burning of fossil fuels degrades the environment of all living things.

The United States should be proud of its unique national consensus on the importance of the environment. But consensus and dedication will not be sufficient as

the human population of the Earth increases and more and more of us become consumers. Nor will current technologies that focus on conservation and recycling be enough. We will need to adopt what we might call supply-side environmental strategies ....alternative sources for energy and materials.

Fortunately, the genetic technology discovered and developed in the last quarter of the 20th century is providing just such supply-side potential. The genetic engineering of plants is a successful reality. Last summer, millions of U.S. acres were planted with cotton, soybean and corn plants whose DNA contained genes derived from other organisms. These genes protect against crop loss by predatory insects, and decrease substantially the amount of chemical insecticide that farmers need to use. It is estimated that humans will need, in the next 50 years, a quantity of wheat and rice equal to all that produced since our very ancient ancestors began the genetic experiments that gave us domesticated cereal plants. Twenty-five years ago this would have seemed an impossible challenge to the available resources of water and soil, but now genetically engineered plants that grow on brackish water, are a realistic possibility. Experimental projects are developing plants that can manufacture plastics that we now make from petroleum. There is the possibility that fuel oil might, in future, be harvested from engineered plants. We are likely to be able to make vaccines, and some drugs in plants...a whole new breed of herbal medicines. It is likely that we can engineer plants to salvage metals from industrially contaminated sites. Even trees, whose life cycles normally consume many years, can now be genetically altered because of the discovery of plant genes that speed up the flowering cycle to a few months. Some people are imagining constructing trees with increased cellulose content. This would decrease the number of trees and the amount of noxious chemicals needed to supply our insatiable demand for paper.

In each of these instances, and others, genetically engineered plants will yield unique, and cost-effective ways to harvest the sun's energy for human purposes.

Many people find these scenarios worrisome. Here in the U.S., we have tried to deal with the realistic concerns about genetically engineered plants through careful experiments and tests, through monitoring and regulation. This has allowed these new, supply-side approaches to environmental issues to proceed safely. In contrast, in Europe, fields of genetically engineered plants are frequently destroyed by people who are also fervently dedicated to improving the environment. They have vehemently opposed the importation of genetically engineered plants and plant-products like corn and soybean from the U.S. In less than a year, the Swiss, for example, will vote on a proposal to ban virtually all genetically engineered plants and animals. Many of our European friends and colleagues, and some people in our own country are sympathetic. They are unwilling to rely on rigorous, governmental monitoring and control of the potential problems associated with genetically engineered organisms. Moreover, many of the naysayers are disturbed, not so much by realistic and controllable potential problems, but by a belief that there is something unnatural about these genetic technologies. But in fact, organisms have been exchanging genes in nature probably since living things first appeared on Earth about 3.7 billion years ago. And human beings have been manipulating the genes of other organisms at least since agriculture began in prehistory, albeit by less precise methods. We all, including the naysayers, live lives that are completely dependent on 'unnatural' things. The history of our species is a history of adopting 'unnatural' technologies if they are useful, and we want them, and they don't do too much harm---- and sometimes even if they do a lot of harm. Once, recently, when someone was being very critical of all technology because of its potential for misuse, I asked her if she would like to give up her cheap nylon panty hose. She didn't understand my question. She had never thought about the fact that manufacturing the hosiery was a very high-tech process.

The unease about genetic engineering of plants is of a piece with concerns about the genetic engineering of animals and especially humans, as well as other reproductive technologies. Here too, there are tough, substantive issues as well as ill-defined unease. We heard a good deal of both of these a couple of weeks ago when the Scottish sheep named Dolly hit the front pages.

One perplexing set of concerns is in the clash of some religious and philosophical beliefs with scientific goals and practical, beneficial opportunities. For example, some genetically engineered animals are essential research tools for the investigation of human disease, while others can be used to produce valuable therapeutic agents. These are the goals that motivated the scientists who produced Dolly. Yet a coalition of U.S. religious leaders has sought to impede these developments by proposing a ban on the patenting of human genes, cells, and organs, and other genetically modified organisms. Surely they will extend their campaign to include clones like Dolly, and are also likely to want to ban such clones altogether. Their argument is that genes, cells, and organisms, are creations of God and not inventions of man. But scientists who synthesize genes by chemical techniques in their laboratories and recognize the near identity of human genes with those of other species, cannot think of human DNA molecules as holy. Moreover, it is, in a sense, genes (that is DNA) that build cells and organisms.

Reaping the benefits of the new technologies requires commercial sector participation, and that commitment may not occur without the protection of financial investments that patents provide. We shall have to find a way to resolve the conflict between religious and scientific views about molecules and biological organisms. We shall also need to resolve the conflict between religious precepts and the moral imperative to do all we can to relieve human suffering and improve the human condition. This

conflict is of course not new. In the late 18th century, for example, a great debate occurred in our emerging nation about the morality of inoculations to limit the devastation of small pox. Some religious leaders argued that if God had not wanted humans to suffer from it, He would not have created small pox. George Washington himself had to force a political decision to inoculate American troops when the disease threatened more devastation than British guns. Such arguments still appeal to some among us, as we have seen in some reactions to AIDs.

There are other problems that need resolution if we are to make constructive use of genetic research. Already we are able to identify genetic changes that are associated with certain diseases or predispositions to particular diseases. Some of these, like cystic fibrosis and hemophilia and certain cancers are inherited disorders. Other cancers are related to changes that occur in an individual's DNA in the course of a lifetime but are not inherited. Increasingly sophisticated screening techniques (that depend on an enzyme from the Yellowstone thermophiles) permit identification of individuals carrying such gene changes, even before disease is manifest. Such information will engender personal and familial anxieties and societal stress that need sympathetic, informed counselling. We will need to assure that individuals are protected against discrimination in employment and in health and life insurance. This is particularly important now for at least two reasons. First, although diagnostic genetic screens can be definitive, we lack sufficient understanding to translate that information into reliable prognoses for individuals. Second, there are no effective therapies for most of these disorders. Early in the 21st Century, when the project to determine the entire structure of the human genome is completed, this problem will be even more acute because many more genes and associated diseases will be identifiable. It is likely that none of us will turn out to be perfect-----assuming we knew what perfect means.

Beyond these difficult challenges, and perhaps most deeply and universally felt, is concern that modern biological research and the institution of broad-based genetic testing will spur a malevolent renewal of interest in eugenics. Surely, such consideration troubles most of those who have written in recent weeks about Dolly's significance for our species. Differences in the depth of concern about eugenics help us to understand European attitudes toward genetic engineering. Europeans hold more immediate memories of its dangers than do most Americans. We are more likely than they to forget the evil role that eugenics and geneticists played in the Holocaust.

In thinking about this issue we need to distinguish carefully between two very different ways of using genetic and reproductive techniques. The first is unrelated to eugenics. It is therapeutic intervention in diseased individuals or fetuses...an approach which, if we can get it to work, appears to have broad acceptability. Gene therapy itself has no effect on inheritance because it deals with body cells; in mammals like ourselves, the cells that give rise to eggs and sperm-the germ cells-are sequestered very early in the development of an embryo. The second, which is relevant to eugenics, has to do with altering genes in eggs or sperm, which are the vehicles for passing genes from one generation to the next and it has to do with cloning of humans.

In order to carry out germ cell manipulations, at least with the technology currently in use for experimental animals like mice, or farm animals like pigs and sheep, the germ cells must be removed from the body and handled under laboratory conditions before returning to a mother. There are, in fact, scientific reasons for believing that alteration of genes in human eggs and sperm, even were it to become a possible and reproducible technique, could not achieve a reliably improved genome and would therefore not be a very good tool for eugenics. New mutations are continually generated in all our cells, body and germ cells alike. And subsequent sexual reproduction will again

generate unique mixtures of genes whose interactions are so complex that it is difficult even to imagine making them predictable.

Cloning of course by-passes sexual reproduction at least in one generation. Dolly's genome is likely to be almost identical to the genome of the sheep udder cell that donated its DNA. She should not harbor many new or unique combinations of genes - although it's possible that she carries a few. This is because the DNA in the donor cell may not be a perfect duplicate of the DNA that initiated the development of Dolly's biological mother. Body cells like udder cells are many cell generations removed from the fertilized egg cell. At each cell generation some number of mutations collect at random in the genome. Some of these could be lethal during development and this may explain, in part, why only one Dolly was produced from 277 tries. Other such mutations may cause her problems later in life - premature aging, infertility, or cancer are examples. We shall want to follow her progress carefully. We will also want to know whether the Dolly experiment is reproducible. This knowledge is an essential basis for any discussion of human cloning.

Moreover, what works for sheep may or may not work for humans. Any experiment designed to find out if an adult human can be cloned requires making such a clone and being prepared for a bad outcome. Do we, as a society, or any individuals among us, want to do that experiment?

Many scientists agree that in the absence of any indisputable therapeutic utility, and without absolute assurance of complete safety, attempts to modify human eggs and sperm by genetic engineering should not even be considered. At present, such assurances are impossible. I believe that a similar consensus is likely to emerge with respect to cloning humans. Thus, it is unlikely that any resurgent interest in eugenics will come

from the scientific community. As far as I know, there is then no reason to infer evil intent by scientists. There is, however, every reason to be wary and to discuss these questions widely. As the science progresses, the broad community must carefully decide what uses are important, desirable, and acceptable. The need for a well-informed citizenry to carry out this discussion is one reason to encourage widespread improvement in science education in America.

During this talk I have repeatedly said "we know this" or "we know that" about the world around us. But of course, no one knows all these things, or the many other promising scientific and technical developments I have not mentioned. Even scientists know very little about research outside their own fields. Biologists don't know much about galaxies and astronomers little about genes. But as scientific knowledge gets converted into useful technology, all of us must participate in the debates about the relative potentials each technology has for good and for harm. Not everyone will have the bent or want to be a scientist. But our definition of an educated person must now include a sound appreciation of science and technology so that they can be wisely and equitably used. Otherwise we risk unwise political decisions, decisions that are incompatible with the natural world or a healthy environment, or political decisions that deny us useful technologies on spurious, indefensible grounds. This will be an interesting debate. Cautious, thoughtful people will want to move slowly. Luddites will not want to move at all. Many people will be eager for any new technology if they think it can cure loved ones, or improve capabilities deemed desirable, or make a buck. We need only think about the illicit use of human growth hormone to grow tall and brawny athletes, once it became cheap and available through recombinant DNA technology. And there are bound to be a few people with sufficiently large egos and little understanding of the great benefits of the genetic crap game to want to clone themselves.



Already now, and increasingly in the future, the greatness of nations will be measured by the knowledge and technology they produce and the wisdom with which they put them to use. This measure will apply to national economies, to military power, to intellectual influence and even to the arts which more and more mine science and technology for creative projects and certainly for distribution. Our country has led the world in increasing knowledge and technology and we have the best shot around for maintaining that leadership. The proof is in the constant flow of newcomers who emigrate here and enrich our society, because they know that this is the place to do science, to develop technology. The United States is the leader not because we are smarter than other nations, or because we are richer, but because we are a freer people. Freedom breeds the optimism that is the most fertile ground for science and for innovation.

In 1994, Václav Havel tied his forebodings about the new millennium to what he saw as the responsibility of science for the disappearance of God from the world--and with Him, the source of the set of values embodied in the American Constitution and Bill of Rights. But such pessimism conflicts profoundly with that very same set of values. Science, on the other hand, affirms the optimism of American values. We should accept Giamatti's challenge and work "to give definition--shape and contour--to what is around us." Our understanding of the natural world must be an integral part of that definition, as I have tried to show. And that understanding clearly tells us that the history and future of the universe and of our planet have nothing to do with the convenient ways in which we enumerate the trips that Earth makes around the sun.